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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,038	MEYER, OLIVIER	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 7-26* is/are pending in the application.

4a) Of the above claim(s) *22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 7-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Action is in response to the communication filed on 2/02/04. The amendment has been entered. Claim 1 has been amended. Claims 2 and 6 have been cancelled. Claims 1, 3-5 and 7-26 are currently pending in the application and are addressed herein.

Priority

2. It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/246,090, filed 11/7/2000. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen

months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France on 6/16/2000. It is noted, however, that applicant has not filed a certified copy of the application (No. 00-07604) as required by 35 U.S.C. 119(b).

Claim Objections

4. Claim 16 is objected to because of the following informalities: It appears that claim 16 should depend on claim 14 rather than claim 11, because claim 14 includes the limitation "adjuvant" which is not present in claim 11. Appropriate correction is required.

5. Claim 21 is objected to because of the following informalities: Claim 21 depends on any of claim 1-7, however, claims 2 and 6 have been cancelled; therefore, claim 21 should not depend on claim 2 or 6. Appropriate correction is required.

Election/Restrictions

6. This application contains claims 22-26 drawn to an invention nonelected with traverse in the Paper filed 10/30/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

7. Additionally, Applicants elected, with traverse the species: Hexadecylphosphocholine (HPC or HePC) and IL-2 in Paper No. 8 (10/30/02).

8. Claims 1, 3-5 and 7-21 are examined herein.

Claim Rejections - 35 USC § 103

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 1, 3-5, 7-17, and 19-21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Egilmez et al. (Gene Therapy, Vol. 3, p. 607-614; 1996, cited in IDS) in view of Vehmeyer et al. (Cellular Immunology, Vol. 137, p. 232-238; 1991), for the reasons of record which are reiterated below for clarity.

The instant claims are drawn to a combination product comprising a nucleic acid encoding a polypeptide of interest and at least one phospholipid having a particular structural

limitation. It is noted that a species election was set forth in a previous Office Action and Applicants elected the following species: IL-2 (as the elected species of polypeptide of interest) and Hexadecylphosphocholine (HePC) (as the elected species of phospholipid) (see Paper No. 8).

Egilmez teaches a composition comprising cationic-liposome nucleic acid complex wherein the nucleic acid comprises a plasmid vector which operably encodes IL-2 (e.g., see abstract and p. 608, column 1). Egilmez teaches that human IL-2 encoding nucleic acid is complexed with DC-cholesterol liposomes (a cationic liposome which associates with the nucleic acid of interest and which is capable of integrating into a liposome) which can be transferred to tumors in vivo resulting in suppression of the tumor growth (e.g., see abstract). Egilmez also indicates that the composition can be diluted in sterile DMEM (a pharmaceutically acceptable vehicle) and then injected into tumors in mice (e.g., see p. 613, second column).

Egilmez does not teach that the composition comprises a phospholipid which meets the structural limitations set forth in the claims, such as Hexadecylphosphocholine (HePC) (the elected species).

However, Vehmeyer teaches Hexadecylphosphocholine (HePC) an antitumor compound having immunostimulatory activity such that it enhances T-cell responses via IFN-gamma induction, but only when HePC is used in combination with IL-2 (e.g., see abstract and p. 232 last paragraph, and p. 233 under "Results") Vehmeyer specifically teaches, "In no case was a significant IFN-g production found in the presence or absence of HePC when IL-2 had been omitted from the cultures" (see p. 233 under "Results")—indicating the critical importance using HePC in combination with IL-2.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to modify the composition taught by Egilmez such that the composition comprised HePC (in addition to the nucleic acid encoding IL-2 and DC-cholesterol liposome) wherein the components are formed into a complex that can be delivered to tumors in order to suppress tumor growth with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings of Egilmez and Vehmeyer because Vehmeyer indicates that the combination of HePC and IL-2 induces IFN-g and enhances T-cell antitumor responses (e.g., see abstract and p. 232 last paragraph).

It is noted that claim 1 indicates that the polypeptide and phospholipid of interest have cytotoxic activity. It is respectfully pointed out that the claim is drawn to a product (i.e. a combination product) and the limitation that the polypeptide and phospholipid have cytotoxic activity is merely a functional limitation. Therefore, any composition that meets the structural limitations of the claims would by necessity have the desired function. However, in the instant case, it is clear that the prior art indicates that IL-2 and HePC have cytotoxic activity when used together (e.g., see Vehmeyer, p. 232, abstract).

Response to Arguments

11. Applicant's arguments filed 2/02/04 have been fully considered but they are not persuasive.

12. Applicants argue that in the present case, 1) the references fail to recite the elements of the claimed invention as amended herein, there is insufficient motivation to modify the cited

references in the manner proposed in the Official Action, and there is no reasonable expectation of success of achieving the claimed invention. (See p. 8 of the Paper filed 2/2/04).

13. Specifically, Applicants argue that Egilmez encompass experiments that were done in SCID mice, i.e., mice that lack immunocompetent B and T cells. (See p. 9). Applicants also contend that Vehmeyer does not disclose or even suggest that HePC and IL-2 enhance T cell antitumor response (See p. 9), and point out that Vehmeyer does not measure T cell activity against tumoral cells. Applicants argue that Vehmeyer does not link the T cell activation of HePC to antitumoral activity, but rather Vehmeyer merely states that further studies regarding HePC activity are needed. Thus, according to the Applicants, the cited references fail to provide the skilled artisan with motivation to modify or combine the references with any expectation of success.

14. In response, Applicants' arguments have been fully considered, but are not persuasive. Regarding the Applicants arguments with respect to Egilmez's experiments in SCID mice, it is acknowledged that the experiments performed by Egilmez were done in SCID mice. It is also acknowledged that SCID mice lack immunocompetent B and T cells. However, it is respectfully pointed out that the SCID mouse is an accepted mouse model for human tumors, wherein human tumor cells are transplanted into the SCID mice. The SCID mice comprising the human tumors must lack immunocompetent B and T cells in order to ensure that the human tumors are not killed by the mouse immune system. Also, the instant claims are drawn to a composition, not to a method of treatment; and furthermore, the rejection of record was not predicated on combining the references in order to administer the composition to a SCID mouse. Therefore, the fact that the SCID mouse does not comprise immunocompetent B and T cells does not preclude the

motivation to combine the references in order to make the claimed composition for use in treating tumors in a human which have immunocompetent B and T cells. With respect to Applicants arguments regarding the Vehmeyer reference. It is acknowledged that Vehmeyer does not measure T cell activity against tumoral cells. However, it is well recognized in the prior art of record that HePC has been proven to exhibit a dose-dependent antitumor activity. See, for example, Hochhuth et al. (Cellular Immunology, 1992; Vol. 141, pp. 161-168) first paragraph on p. 161. In addition, Vehmeyer does teach that HePC is a T cell activator when it is used, in vitro, in combination with IL-2, as acknowledged in Applicants' response (See p. 9). Therefore, Vehmeyer does indicate that HePC in combination with IL-2 activates T cells, as indicated by IFN-gamma production. As such, Vehmeyer does indicate that HePC and IL-2 in combination can activate T cells. Furthermore, T cell activation would be readily recognized to one of ordinary skill in the art as a desired component in an anti-tumor response in a subject. Since Egilmez indicates that IL-2 can be an effective anti-tumor treatment by activating the immune response (NK cells) and considering that Vehmeyer indicates that HePC in combination with IL-2 activates T cells (helper cells which are known to augment the immune response in an immunocompetent subject) it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the references in order to make the claimed composition wherein the composition would be useful for treating tumors in an immunocompetent subject, with a reasonable expectation of success.

One of ordinary skill in the art would have a reasonable expectation of success in carrying out the invention as a whole to suppress the growth of a tumor because: 1) IL-2 encoding plasmid/cationic liposomal complex has been shown a an effective anti-tumor agent

(e.g., see Egilmez); 2) HePC has been proven by the totality of the prior art of record to exhibit a dose-dependent antitumor activity; and 3) HePC also has been shown by Vehmeyer to exhibit an HePC-mediated enhancement of T-cell response to IL-2. As such, one of ordinary skill in the art would have expected that the combination of IL-2 encoding DNA/cationic lipid complex and HePC would enhance anti-tumor activities against a tumor in a cancer patient.

15. Claims 1, 11, 16-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Egilmez et al. (Gene Therapy, Vol. 3, p. 607-614; 1996, cited in IDS) in view of Vehmeyer et al. (Cellular Immunology, Vol. 137, p. 232-238; 1991), as applied to claims 1, 11 and 16 above, and further in view of Bischoff (WO 98/08489) for the reasons of record which are reiterated below for convenience.

As indicated above, Egilmez teaches a composition comprising cationic-liposome nucleic acid complex wherein the nucleic acid comprises a plasmid vector which operably encodes IL-2 (e.g., see abstract and p. 608, column 1). Egilmez teaches that human IL-2 encoding nucleic acid is complexed with DC-cholesterol liposomes (a cationic liposome which associates with the nucleic acid of interest and which is capable of integrating into a liposome) which can be transferred to tumors in vivo resulting in suppression of the tumor growth (e.g., see abstract). Egilmez also indicates that the composition can be diluted in sterile DMEM (a pharmaceutically acceptable vehicle) and then injected into tumors in mice (e.g., see p. 613, second column).

Egilmez does not teach that the composition comprises a phospholipid which meets the structural limitations set forth in the claims, such as Hexadecylphosphocholine (HePC) (the elected species).

Vehmeyer teaches Hexadecylphosphocholine (HePC) an antitumor compound having immunostimulatory activity such that it enhances T-cell responses via IFN-gamma induction, but only when HePC is used in combination with IL-2 (e.g., see abstract and p. 232 last paragraph, and p. 233 under "Results"). Vehmeyer specifically teaches, "In no case was a significant IFN-g production found in the presence or absence of HePC when IL-2 had been omitted from the cultures" (see p. 233 under "Results")—indicating the critical importance using HePC in combination with IL-2.

Neither Egilmez nor Vehmeyer teaches that the combination product complex has a charge ratio in the range of 0.05-20 (claim 17) or that complex has a diameter of between 20 and 800nm (claim 18).

However, Bischoff teaches a cationic lipid-nucleic acid complex wherein the cationic lipid is preferably DC-cholesterol (e.g., see p. 10 lines 8-11) and wherein the mean diameter size of the complex is less than 400nm, and in most cases less than 200nm (e.g., see p. 25, lines 5-6 and claim 6); and have a mean charge ratio that preferably are in the range of 1-20 (see p. 14, lines 25-27). Bischoff indicates that the cationic lipid-nucleic acid complexes having a charge ration in the range of 1-20 and that have a mean diameter less than 400nm were able to deliver the nucleic acid of the complex into cells in vivo (e.g., see Example 3, p. 26-27).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to modify the composition taught by Egilmez such that the composition comprised HePC (in addition to the nucleic acid encoding IL-2 and DC-cholesterol liposome) wherein the components are formed into a complex (as indicated above) and to further modify the composition such that the mean diameter size of the complex was less than 200nm (i.e., in

the range of 20 and 800nm) and such that the charge ratio of the complex was in the range of 1-20, with a reasonable expectation of success.

The motivation to modify the complex made by combining the teachings of Egilmez and Vehmeyer is provided by Bischoff who indicates that cationic lipid-nucleic acid complexes have a charge ratio in the range of 1-20 and with a mean diameter size of less than 200nm are able to deliver the nucleic acid encoding polypeptide of interest into cells in vivo. It is noted that Egilmez does not explicitly indicate any particular diameter size for the complex, or any particular charge ratio for the complex.

Response to Arguments

16. Applicant's arguments filed 2/02/04 have been fully considered but they are not persuasive. Applicants argue that Egilmez et al. and Vehmeyer fail to provide the skilled artisan with motivation to modify the references, motivation to combine the references and with an expectation of success, for the reasons indicated above. Furthermore, Applicants contend, Bischoff fails to remedy the deficiencies of Egilmez et al. and Vehmeyer. It is asserted that Bischoff fails to provide the motivation to alter the cited references and expectation of success that the other cited references fail to provide and, as a result, the three cited references, alone or in combination, do not render the claimed invention obvious.

In response, Applicants arguments have been fully considered but are not persuasive. As indicated above, Egilmez and Vehmeyer render instant claims 1, 11 and 16 obvious. Furthermore, Bischoff teaches a complex comprising a cationic lipid (preferably DC-cholesterol) and wherein the mean diameter size of the complex is less than 400nm, and in most cases less than 200nm; and have a mean charge ratio that preferably are in the range of 1-20 (as previously

indicated and reiterated above). Bischoff also indicates that the complex has a charge ratio in the range of 1-20 and that have a mean diameter less than 400nm were able to deliver the nucleic acid of the complex into cells in vivo.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the cited references to make the claimed composition with a reasonable expectation of success. Furthermore, Bischoff contains the motivation to make the desired changes because Bischoff teaches the nucleic acid-lipid complexes having a diameter and charge ratio as claimed are the appropriate size for in vivo administration of the complex.

Conclusion

17. No claim is allowed.

18. It is respectfully pointed out that the instant application contains claims 22-26 drawn to an invention nonelected with traverse in the Paper filed 10/30/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

19. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art Unit 1635

DAVE T. NGUYEN
PRIMARY EXAMINER